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SYNTHESIS AND EVALUATION OF SOME NEW THIAZOLE / OXAZOLE DERIVATIVES FOR THEIR BIOLOGICAL ACTIVITIES

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ABSTRACT

The Benzimidazoles, 1,2,4 triazoles, thiazolidinones, oxadiazoles, pyridine and pyrimidine nucleus has diverse pharmacological activities such as antibacterial, anthelmintic, antifungal etc. The thiazole nucleus is also known to possess various biological activities viz. antidepressant, hypertrophy, cardiac, bactericidal, anaesthetic and antifungal activity. The aim of this work is to study the effect of three methoxy group on the course of the reaction with substituted thiazole/oxazole nucleus and on the antibacterial & antifungal activity of the synthesized products. The synthesized compounds were investigated against Staphylococcus aureus, B.subtilis, P. Aeruginosa, and E.coli for antibacterial study and against C. Albicans, Aspergillus Niger for antifungal activity.

KEYWORDS:- Thiazole, Oxazole, trimethoxybenzaldehyde, Antifungal, Antibacterial activity.

INTRODUCTION

The greatest progress in medicinal chemistry has come from the application of modern biochemistry to its problem. The approach to the study and design of medicinal agents has centered primarily on the gross chemical structure of natural and synthetic compounds having established biological action.

Modifications of the basic structure are obtained by chemical synthesis and the effect of these change in biological response are used to compile structure activity relationship. These relationships are intended to serve as a guide in the interpretation of the structural feature

essential for a given type of drug activity and also in the design of new agents of similar biological activity.

A currently promising approach is the attempt to relate certain physio chemical properties of drugs to their mode of action which leads to an understanding of drug action or result in the development of more effective drug.

The present investigating studies includes the chemistry and application of highly interesting and significantly useful sulphur and nitrogen molecules. Among the various branch of organic, sulphur and nitrogen chemistry, the chemistry of thiazole, pyrimidine, pyridine, thiadiazoles, oxadiazoles, tetralin occupy a position of importance.

There is a great need for better antifungal drugs, made pressing by the increased incidence of the systemic dissemination of fungal infections in immuno suppressed patients. The application of these compounds is really main fold and versatile. They are being used as CNS[1-5] active, antituberculous[6], antispasmodic[7-8], antifungal[9-15] and antibacterial activities.

Imines are also known to possess biological activity [16]. It has been reported that the presence of electron donating groups like hydroxyl, methoxy, etc. in the phenyl nucleus increases the activity of the parent compound.

The facts were also considered during heterocyclic derivatives preparation that many phenols and compounds with phenolic groups have anti-fungal potency.[17-19]

Substituted benzylidine/oxaquinazolin[20] phenyl semicarbazide & quinazolinone heterocyclic derivatives[21] shows antibacterial and antifungal activities.

Some triazole derivatives of gallic acid[22] and 1,2,4 triazoles derivatives[23] has been reported for their antibacterial and antifungal activities.

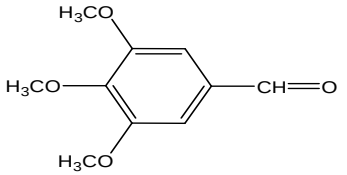
Pyrimidine containing furanose derivatives[24] and substituted pyrimidine derivatives[25] has been reported to possess for antifungal, antioxidant, anticancer activities.

1,3,4 oxadiazoles[26], thiazolidinone derivatives[27],2,4 di substituted thiazoles[28], thiazoles and 1,3,4 oxadiazoles[29] hybrid heterocycles has potential antimicrobial and antifungal activities.

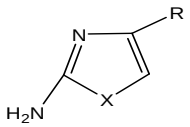
Literature review reveals that Pyrrole derivatives[30], pyrazine and related heterocycles[31], tetrazoles derivatives[32], pyranopyrazole derivatives[33], azoles and azine derivatives of tertiary butyl carbazate[34], Schiff base derivative[35], chalcones derivatives of heterocyclic compounds[36,37], heterocyclic based 6-chloro pyridazine thiones[38], substituted 3-indolylthiophene derivatives know for potential antimicrobial and antifungal activities[39].

Lots of work has been done on thiazole & oxazole nucleus with potential biological activities like antifungal, antibacterial, anti-inflammatory, antiviral, antidiuretic, antiviral anticancer and antioxidant activities. The present work describes the effect of three methoxy group in the carbon phenyl nucleus on the course of reactions with substituted thiazole /oxazole nucleus and on the antibacterial, antifungal activities of the synthesized products.

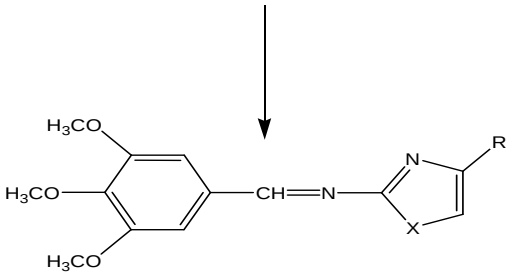
Keeping all the view from the literature study and facts in mind the present work describes the condensation of 3,4,5 trimethoxybenzaldehyde[40] with 2-amino thiazole /4`-(p-subst/unsubst)-phenyl thiazole/ oxazole and evaluated for antibacterial & antifungal activity according to scheme 1.



3,4,5 trimethoxy Benzaldehyde



2-Amino substituted Thiazole/Oxazole



N-(3,4,5-trimethoxybenzylidene)- 4-substituted thiazol/oxazol-2-amine

(1 - 14)

When X= S,Thiazole

Where 1. R= H
2. R= -C6H5
3. R= -C6H4Cl
4. R= -C6H4F
5. R= -C6H4NO2
6. R= -C6H4OCH3
7.R= -C6H4OH

When X= O,Oxazole

Where 8. R= H
9. R= -C6H5
10. R= -C6H4Cl
11. R= -C6H4F
12. R= -C6H4NO2
13. R= -C6H4OCH3
14. R= -C6H4OH

(Scheme-1)

MATERIALS AND METHODS

All the melting points were determined in open capillary tubes. IR spectra were recorded in solid state using KBr pellet method. The spectra were recorded on Perkin Elmer FT-IR spectrophotometer (model RX-1). The PMR spectra were recorded in DMSO-d6 solvent at room temperature using TMS as reference compound. The spectra were recorded on Perkin Elmer Model 32 NMR spectrometer at 300MHz at CDRI Lucknow.

The reactions were monitored by TLC. The required 3,4,5 trimethoxybenzaldehyde and 2-Amino-4-[p-subst/unsubst] phenyl thiazoles / oxazoles were prepared by know method. Procedure for one compound of each step has been described in sequel. The physical Data of compounds are given in Table 1.

Table-1 Physical Data of Compounds

Compd No.	Nature of Ar-NH_2	Yield (%)	M.P (°C)	Molecular Formula
1	2-Amino thiazole	**85**	**145**	$C_{13}H_{14}N_2SO_3$
2	2-Amino-4-phenyl thiazole	**87**	**152**	$C_{19}H_{18}N_2SO_3$
3	2-Amino-4-(p-chloro) phenyl thiazole	**81**	**160**	$C_{19}H_{17}N_2SO_3Cl$
4	2-Amino-4-(p-fluoro) phenyl thiazole	**84**	**175**	$C_{19}H_{17}N_2SO_3F$
5	2-Amino-4-(p-nitro) phenyl thiazole	**79**	**192**	$C_{19}H_{17}N_3SO_5$
6	2-Amino-4-(p-methoxy) phenyl thiazole	**73**	**171**	$C_{20}H_{20}N_2SO_4$
7	2-Amino-4-(p-Hydroxy) phenyl thiazole	**73**	**165**	$C_{19}H_{18}N_2O_4S$
8	2-Amino-oxazole	**89**	**136**	$C_{13}H_{14}N_2O_4$
9	2-Amino-4-phenyl oxazole	**81**	**139**	$C_{19}H_{18}N_2O_4$
10	2-Amino-4-(p-fluoro) phenyl oxazole	**76**	**157**	$C_{19}H_{17}N_2O_4Cl$
11	2-Amino-4-(p-fluoro) phenyl oxazole	**75**	**170**	$C_{19}H_{17}N_2O_4F$
12	2-Amino-4-(p-nitro) phenyl oxazole	**78**	**183**	$C_{19}H_{17}N_3O_6$
13	2-Amino-4-(p-methoxy) phenyl oxazole	**80**	**168**	$C_{20}H_{20}N_2O_5$
14	2-Amino-4-(p-Hydroxy) phenyl oxazole	**79**	**170**	$C_{19}H_{18}N_2O_5$

Preparation of N-(3, 4, 5 tri methoxy Benzylidene)-4-subst/unsbst thiazol /oxazole-2-amine

3,4,5 trimethoxybenzaldehyde (19.6gm,0.1 mol) and 2-amino-4-phenyl thiazole (1.76gm,0.1mol) were taken in benzene (100ml) in a R.B flask (250ml) fitted with Dean & Stark apparatus. The mixture was refluxed till water (1.8 gm, 0.1mol) was separate out. The mixture was then cooled to obtained the crude product which was recrystallize from ethanol to get white crystals of N-(3, 4, 5 tri methoxy Benzylidene)-4-subst/unsbst thiazol /oxazole-2-amine.

Yield: 92%, M.P 159°C. IR (KBr): 1110cm^{-1} (due to C=S), 1605 cm^{-1} & 1250 cm^{-1} (due to C=N & C-N), 1600-1575cm^{-1} (due to azomethine proton)

PMR: δ 3.94 (9H, due to methoxy protons), δ 8.2 (singlet, due to azomethine proton), δ 7.1 (s, 2H), δ 9.85 (s, 1H), δ 7.5 (m, 5H, Ar-H), δ 6.5 (s, CH)

Synthesis of 2-Amino - Thiazole

A solution of 76 gm of thiourea in 200 ml of warm water is placed in 500ml three necked flask equipped with dropping funnel ,mechanical stirrer and reflux condenser.143 gm of α,β-dichloroethyl ether is added and the mixture is heated under gentle reflux with stirring for 2 hrs. As the reaction proceeds, the two layers gradually merge. To the cold solution, sufficient solid NaOH is added to liberate 2-Amino Thiazole from its salt. Ether is added to dissolve the product and ether is evaporated.2-Amino Thiazole is recrystallized from ethanol.

M.P.: 90- 91^{0}C.

IR (KBr): 1255 cm-^{1} (due to C-N), 694 cm-^{1} (due to C-S-C), 1615 & 1535 cm-^{1}(due to C=N)

PMR: δ 6.6 (s, 1H, due to -CH), δ 7.1 (s, 1H, due to -CH), δ 11.4 (d, 2H).

Synthesis of 2-Amino-4-phenyl Thiazole

A mixture of acetopheneone (12.0gm, 0.1mol), thiourea (15.2gm, 0.2mol) and iodine (25.4gm, 0.1mol) was heated for 10 hours on a steam bath. The crude reaction mixture was cooled and repeatedly extracted with ether to remove unreacted acetopheneone and iodine. The residue was then dissolved in hot water and filtered to remove sulphur and other impurities. The solution was then moderately cooled and made alkaline with conc. Ammonia.2-amino-4-phenyl thiazole, thus precipitated was collected and recrystallized from diluted ethanol as long colourless needles.

M.P.: 149^{0}C.

IR (KBr): 1255 cm-^{1} (due to C-N), 694 cm-^{1} (due to C-S-C), 1615 & 1535 cm-^{1}(due to C=N)

PMR: δ 6.6 (s, 1H, due to -CH), δ 7.5 (m, 5H, Aromatic), δ 11.35 (d, 2H,-NH_2).

Synthesis of 2-Amino-4-phenyl Oxazole

A mixture of 2-bromo-1-phenylethanone (1.0 mmol), urea (1.0 mmol) and PEG (0.5mL) was stirred at room temperature until completion of the reaction (monitored by thin layer chromatography). The mixture was washed with water (4mL) extracted with ethyl acetate (3 X 15 ml); the organic phase was separated, dried over anhydrous sodium sulphate, and

filtered. The solvent was removed under vacuum. The crude product was purified by silica gel column chromatography using ethyl acetate-petroleum ether (1:1).After extraction with ethyl acetate, the solution of H_2O and PEG 400 was concentrated.

B.P.: 113-115^{0}C

IR (KBr): cm-^{1} 3432, 2975, 1624, 1388.

1H NMR: (300 MHz, CDCl3): δ 7.52–7.47 (m, 2H, ArH), 7.33–7.28 (m, 2H, ArH), 7.09 (m, 1H, ArH), 6.74 (s, 1H, oxazole), 5.15 (br s, 2H, NH2).

Similarly, 2-Amino-4-p-chloro/fluoro/nitro/methoxy/hydroxyl phenyl thiazoles /oxazoles were prepared.[41-43]

RESULTS AND DISCUSSIONS

Antibacterial & Antifungal Screening

All the synthesized compounds were screened for their Antibacterial properties against Staphylococcus aureus, B.subtilis (gram positive bacteria), P. Aeruginosa, E.coli (gram negative bacteria) & Antifungal Properties against C.albicans, Aspergillus Niger. The activities of the synthesized compounds were tested by cup plate method, using a sterile cork borer of about 5 mm diameters. Wells were made in each petri dish using sterile syringe injected 0.1 ml of standard control and test into the cups. After injection the petri dishes were kept at room temperature for 24 hrs. For uniform diffusion of the agent to occur in seeded in agar medium. The petry dishes Incubated at 37±0.5 °C for 24 hrs.After 24 hrs. diameter of inhibition in millimeter was compared with standard drug. Amphicillin (100 µgm/ml) used as standard for bacteria and ketoconazole (100 µgm/ml) used as standard for fungi. The zone of inhibition was measured in mm to estimate the potency of synthesized compounds as given in Table 2.

Table 2: Screening Results of the newly synthesized Compounds Antibacterial & Antifungal Activity

Inhibition Zone (mm)						
Comp'd no.	**Gram + ve Bacteria**		**Gram - ve Bacteria**		**Fungi**	
	S.aureus	**B.subtilis**	**P. Aeruginosa**	**E.coli**	**C. albicans**	**A.niger**
1	7	5	11	10	9	10
2	10	8	9	13	8	9
3	18	20	19	17	18	16
4	20	22	17	18	19	17
5	15	14	12	15	17	18

6	17	16	16	16	11	12
7	19	17	18	17	12	11
8	6	9	11	8	13	12
9	9	11	13	9	13	11
10	16	17	17	16	12	14
11	17	18	18	16	13	11
12	14	13	11	14	17	16
13	16	18	17	18	11	12
14	17	16	16	17	10	9
Ampicillin	**22**	**24**	**20**	**18**	-	-
Ketoconazole	-	-	-	-	**20**	**18**

Zone of inhibition measured in mm (for Antibacterial compounds)

1. 11-15 mm: moderate activity
2. >15 mm: strong activity

Zone of inhibition measured in mm (for Antifungal compounds)

1. 11-15 mm: moderate activity
2. >15 mm: strong activity

From the activity Data (Table 2), we concluded that compound No 3,4,6,7,10,11,13 & 14 showed maximum inhibition against all the four strains Staphylococcus aureus, B.subtilis, P. Aeruginosa, E.coli & compound No 5 & 12 showed moderate activity against all the four strains compound number 1,5,8,9,12 shows moderate activity against P. Aeruginosa & compound number 2,5,12 shows moderate activity against E.coli.

From the above antibacterial screening data the compounds containing fluoro, methoxy & hydroxyl groups at para positions exhibited very good activity against both the strains.

The synthesized compounds were also evaluated for Antifungal activity against C. Albicans, Aspergillus Niger and found that compound No 3, 4, 5 & 12 showed maximum inhibition against both fungi and compound No 6, 7, 8, 9, 10, 11 & 13 showed moderate activity against both the fungi.

CONCLUSIONS

From the above antibacterial & antifungal screening data the compounds containing nitro group & fluoro at para positions exhibited very good activity against both the strains i.e. electron withdrawing group showed maximum inhibition in both the strains.

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